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ORIGINAL RESEARCH

EFFECTIVENESS OF *Citrus sinensis* PEEL ETHANOL EXTRACT COMBINED WITH AMOXICILLIN AS AN ANTIBACTERIAL AND ANTIBIOFILM AGAINST *Staphylococcus aureus*

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ABSTRACT

Introduction: *Staphylococcus aureus is the main bacterium responsible for periapical abscess. Amoxicillin is a commonly used antibiotic to treat bacteria that cause apical abscesses. However, inappropriate use can lead to resistance. This demonstrates the need for herbal alternative therapies combined with antibiotics. Sweet orange peel (Citrus sinensis) has the potential to inhibit bacterial growth and biofilm.* ***Aim:*** *Determining the antibacterial and antibiofilm effects of the ethanol extract of C. sinensis peel in combination with amoxicillin on the growth of S. aureus.* ***Methods:*** *In vitro laboratory experiments with post-test only control group design. The test solutions were 100% ethanol extract of C. sinensis peel, a combination of 600 µg/mL amoxicillin with extract concentrations of 3.125%, 6.25%, 12.5%, 25%, 50%, and 100%, 600 µg/mL amoxicillin, 1,200 µg/mL amoxicillin as a positive control, and distilled water as a negative control. The antibacterial test was performed using the plate count method, and the antibiofilm test was conducted using the microtiter plate biofilm assay.* ***Result:*** *The combination of C. sinensis peel ethanol extract with amoxicillin, starting at a concentration of 3.125%, was able to inhibit the growth of S. aureus. Antibiofilm test results showed that the antibiofilm effect is most effective at the pellicle formation stage. During a 1-hour incubation, concentrations of 3.125% and 6.25% showed statistically significant differences from the negative control. The 100% extract alone can inhibit the growth of S. aureus biofilm. Amoxicillin alone as a positive control did not have antibiofilm effects.* ***Conclusion:*** *The combination of C. sinensis peel ethanol extract with amoxicillin has antibacterial and antibiofilm effects against S. aureus.*

Keywords: *amoxicillin, antibacterial effect, antibiofilm effect, Citrus sinensis peel, periapical abscess, Staphylococcus aureus*

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INTRODUCTION

Maintaining dental and oral hygiene is one way to maintain overall health. According to data from the 2018 Basic Health Research (Riskesdas), dental and oral health problems account for 57.6% of all health problems in Indonesia.[1] When oral cavity problems are not treated quickly, they can lead to various issues, such as a periapical abscess.[2] Periapical abscess is an infection that often occurs as a result of tooth decay and plaque formation, which allows bacteria to penetrate the pulp area into the apical foramen, forming pus.[3]

A periapical abscess is a type of dental infection that occurs when bacteria from the root canal of a tooth spread to the surrounding tissue and cause inflammation.[4] The main cause of periapical abscesses is infection of the pulp and periapical tissue by anaerobic bacteria.[5] Among facultative anaerobic bacteria, *Staphylococcus aureus* is one of the causes of periapical abscesses.[6] *Staphylococcus aureus* is one of the commensal bacteria that initiates attachment in biofilm formation and produces multiple biofilm layers on the glycocalyx layer.[3,7] Biofilm is a collection of microorganisms, including bacteria, that forms on the surface of teeth and is enveloped by Extracellular Polymeric Substances (EPS) produced by the bacteria.[8] When the oral cavity is imbalanced or not well maintained, oral dysbiosis will occur, which refers to the formation of cariogenic biofilm.[9] Biofilm that adheres to the root canal walls will form bacterial colonies and cause infections that spread to the dentinal tubules and root canals. Infection and contamination of the root canals contribute to the formation of a periapical abscess.[10]

Among all classes of antibiotics, amoxicillin is the most commonly used antibiotic to treat Gram-positive and Gram-negative bacteria, especially for treating infections.[11] This drug is bactericidal by binding to penicillin-binding proteins (PBPs) and inhibiting the transpeptidase process.[3] The ability of *S. aureus* to produce β-lactamase enzymes in attacking the β-lactam ring will render antibiotics inactive because it prevents antibiotics from targeting PBP.[3,11] To reduce the resistance of amoxicillin, this antibiotic is often combined with clavulanic acid, often abbreviated as co-amoxiclav, because it contains a β-lactamase inhibitor that protects amoxicillin from hydrolysis. However, co-amoxiclav has several side effects, such as diarrhea, nausea, vomiting, and gastrointestinal discomfort.[12] Our efforts to minimize resistance can be made by combining amoxicillin with natural ingredients as an alternative source in pharmacology.[8]

Sweet oranges (*Citrus sinensis*) are the most popular fruit globally, with more than 143 million tons produced worldwide in 2019. Usually, the peel is not consumed by humans, but is widely used as animal feed or discarded in landfills.[13] In fact, secondary metabolites in the skin of *C. sinensis* contain higher total phytochemical compounds than the edible part of the fruit.[14] The peel of C. sinensis consists of the flavedo, which is the outer part, and the albedo, which is the inner white part. The flavedo fraction contains oil glands and carotenoid accumulations, while the albedo fraction is rich in secondary metabolites, including flavonoids, glucosides, pectins, and pectic enzymes. Flavonoids are the largest group of polyphenolic compounds and can act as antioxidants and antibacterials by denaturing bacterial cell proteins and damaging bacterial cells.[3,13] Due to its high antibacterial effect, *C. sinensis* extract is also widely used in pharmacology as an anti-diabetic, larvicide, antifungal, hypotensive, antioxidant, antiviral, and antimutagenic agent.[15] Therefore, this study aims to determine the antibacterial and antibiofilm effects of the combination of amoxicillin and *C. sinensis* peel

extract as inhibitors of the growth and biofilm formation of *S. aureus*.

METHOD

This study was an in vitro laboratory experiment with a post-test only control group design conducted at the MiCORE (Microbiology Center of Research and Education) Laboratory, Faculty of Dentistry, Trisakti University, from August to November 2024. The research sample used S. aureus ATCC 25923 bacteria obtained from the MiCORE Laboratory, Trisakti University, Jakarta. Ethanol extract of *C. sinensis* peel obtained from BPSI-TROA (Balai Pengujian Standar Instrumen Tanaman Rempah, Obat dan Aromatik) in Bogor, West Java. Before conducting the research, the Trisakti University FKG Ethics Commission issued an Ethical Clearance with letter number 797/S1/KEPK/FKG/6/2024.

Before determining the dose of amoxicillin for the treatment group, the MBC test of *S. aureus* ATCC 25923 was carried out on amoxicillin, and the result was 1,200 µg/mL.[16] This MBC value will be used as a positive control, and 0.5 times the MBC value, namely 600 µg/mL, will be used in combination with various concentrations of *C. sinensis* peel ethanol extract. There were 10 treatment groups in this study, namely *S. aureus* ATCC 25923 bacteria cultured with Brain Heart Infusion Agar (BHI-A) medium with treatment of 100% *C. sinensis* peel, and extract concentrations of 50%, 25%, 12.5%, 6.25%, and 3.125% diluted with distilled water, which will be combined with 600 µg/mL amoxicillin, 600 µg/mL amoxicillin, *C. sinensis* peel extract at 100% concentration, *S. aureus* ATCC 25923 bacteria cultured on BHI-A medium with amoxicillin at an MBC of 1,200 µg/mL as a positive control, and *S. aureus* ATCC 25923 bacteria cultured on BHI-A medium with sterile distilled water as a negative control.

The number of repetitions to be performed in the study is calculated based on Federer's formula; the number of repetitions is 3. The materials used in this study consisted of bacteriological agar (Oxoid), sterile distilled water, *S. aureus* ATCC 25923 bacterial culture; Brain Heart Infusion Broth (BHI-B) (Sigma Aldrich); *C. sinensis* peel ethanol extract; 96% ethanol for analysis, 500 mg amoxicillin powder (PT. Pharma Laboratories); 0.05% w/v crystal violet (Merck), and 50 mmol pH 7 phosphate buffered saline (PBS) (Biomatik). The instruments used consisted of 96-well plates (Nest Biotech); anaerobic jar (Oxoid); autoclave (Tomy); Petri dishes; measuring cups (Iwaki); incubator (Jisico); microplate reader (Safas); microtubes (Onemed); micropipettes (Lambda); tube racks; inoculation needles; Erlenmeyer flasks (Iwaki); vortex (Biosan).

Preparation for this study involved conducting a phytochemical test of *C. sinensis* peel ethanol extract, which was carried out qualitatively by BIOFARMAKA IPB. All instruments and materials were sterilized in an autoclave for 30 minutes at a temperature of 121°C. Bacterial media was prepared by mixing 6 grams of bacteriological agar powder and 14.8 grams of BHI-B powder into a tube containing 400 mL of sterile distilled water, then poured into

16 Petri dishes. The *S. aureus* ATCC 25923 suspension was prepared by taking a pure culture and placing it in a tube containing 10 mL of BHI-B, then incubating it in an anaerobic jar for 24 hours. The turbidity level of the suspension was in accordance with the McFarland 0.5 standard (1.5 x 10^8 CFU/mL). Amoxicillin was dissolved in distilled water to obtain a concentration of 1,000 µg/mL using a vortex.

The antibacterial effect of the combination of C. sinensis bark ethanol extract and amoxicillin was tested using the microdilution and plate count methods. A total of 100 µL of S. aureus ATCC 25923 suspension was distributed into a 96-well plate. Above the bacterial suspension, 100 µL of each treatment group was added and incubated anaerobically for 24 hours at 37°C. After incubation, all treatment groups were diluted 1,000 times with PBS. Five µL of each solution in the treatment group was taken and streaked on BHI-A medium in Petri dishes (triplicate). After incubation for 24 hours at 37°C, each Petri dish was manually counted for bacterial colonies formed.

The antibiofilm effect of the combination of *C. sinensis* peel ethanol extract and amoxicillin was tested using the microtiter plate biofilm assay method. A total of 200 µL of *S. aureus* ATCC 25923 suspension was distributed into 5 wells of a 96-well plate and incubated for 24 hours at 37°C. The supernatant was discarded, leaving a thin layer of biofilm at the bottom of the wells. The 96-well plate was then rinsed twice with PBS. A total of 200 µL from all treatment groups was distributed into the 5 wells mentioned above, and 2 wells without a biofilm layer were incubated for 1 hour, 3 hours, and 24 hours on each 96-well plate. The wells were fixed by passing them over a flame. Then, 200 µL of crystal violet solution was added to each well to stain the formed biofilm, rinsed twice with PBS, and dried. To determine the optical density (OD) formed, the intensity of the crystal violet color was measured using a microplate reader at a wavelength of 490 nm to determine the inhibitory effect on the formation of *S. aureus* ATCC 25923 biofilm.

The data in this study were analyzed using Statistical Product and Service Solution (SPSS) version 27. Before analyzing the data, normality was tested using the Shapiro-Wilk method. If the data distribution was normal ($p>0.05$), a one-way analysis of variance (ANOVA) was performed, followed by a homogeneity test. If there are significant differences in the data ($p<0.05$) within the group, a post-hoc test will be performed using the Tukey Honestly Significant Difference (HSD) method to identify which treatment groups have significant differences.

RESULT

Table 1 shows the results of qualitative phytochemical testing, indicating that ethanol extracts of *C. sinensis* peel contain secondary metabolites, flavonoids, and saponins. The results of the bacterial growth inhibition test in each treatment group were obtained by counting the total number of bacterial colonies formed in all Petri dishes. The antibacterial test showed that 100% ethanol extract of *C. sinensis* peel and combinations of amoxicillin with extracts of various concentrations were able to inhibit the

growth of *S. aureus*. Figure 1 shows the bacterial colonies that formed. It can be seen that the fewest bacterial colonies were formed at a concentration of 6.25%, and the most colonies were formed in all combinations at a concentration of 50%. In inhibiting the growth of *S. aureus*, the statistical results showed the test solution of *C. sinensis* peel ethanol extract at a concentration of 3.125% (49.00 ± 17.09) x 10^5 CFU/mL, 6.25% concentration (30.33 ± 12.34) x 10^5 CFU/mL, 12.5% concentration (72.33 ± 28.15) x 10^5 CFU/mL, 25% concentration (69.00 ± 22.27) x 10^5 CFU/mL, concentration 50% (147.00 ± 70.68) × 10^5 CFU/mL, and concentration 100% (103.33 ± 26.58) × 10^5 CFU/mL. In the results of the 100% ethanol extract of C. sinensis peel, a significant difference was also observed with the negative control, with a value of (92.33 ± 27.32) x 10^5 CFU/mL. Meanwhile, at 600 µg/mL amoxicillin and in the positive amoxicillin control, there was a significant difference compared to the negative control (0 ± 0) x 10^5 CFU/mL.

In the antibiofilm test, the addition of extract to amoxicillin in inhibiting the formation of S. aureus biofilm reduced the OD value compared to the positive control. At an incubation period of 1 hour (Figure 2A), the 6.25% combination showed an antibacterial effect. At the 3-hour incubation period (Figure 2B), all combinations of extract with amoxicillin showed no significant difference from the negative control ($P<0.05$). At the 24-hour incubation period (Figure 2C), it was observed that a combination of amoxicillin with 100% extract was required to produce an antibacterial effect. During all incubation periods, a significant decrease in OD values was observed at a concentration of 100% extract alone, showing good results in inhibiting the growth of *S. aureus* biofilm. It can also be seen that during all incubation periods, amoxicillin, as a positive control, showed OD results that were almost equivalent to or higher than the negative control, indicating that amoxicillin has no antibiofilm effect.

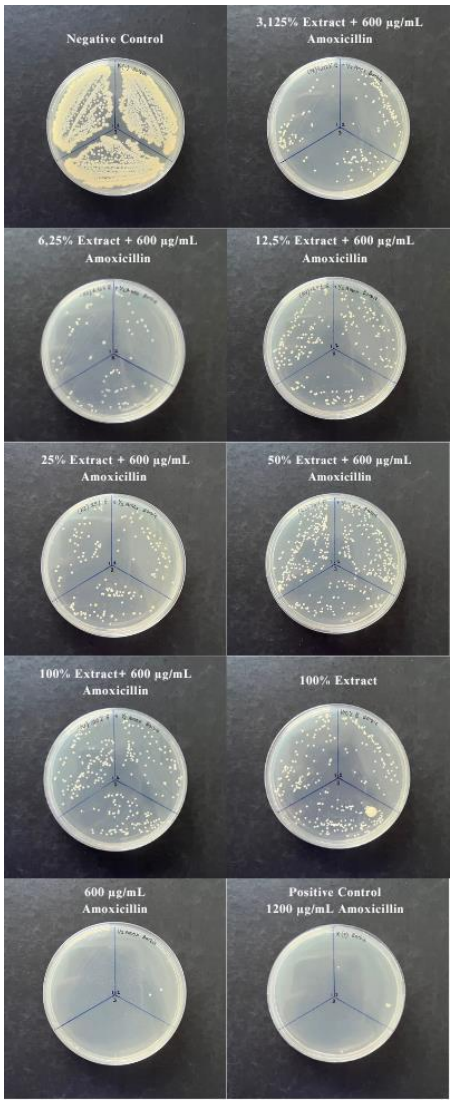
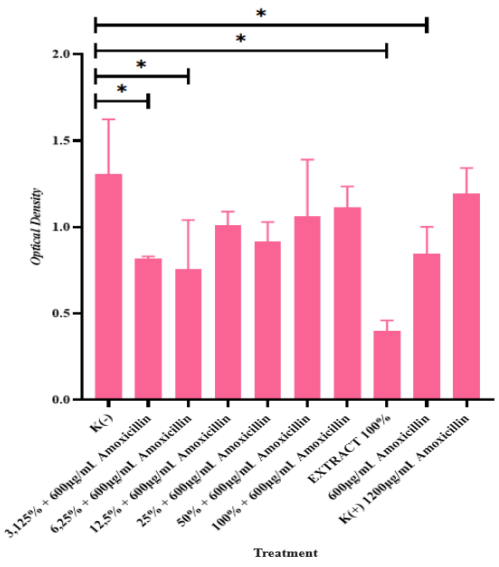
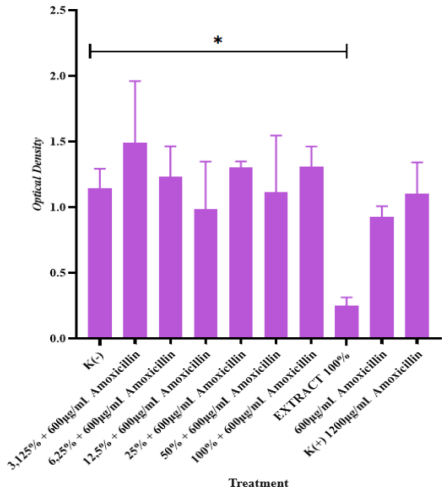


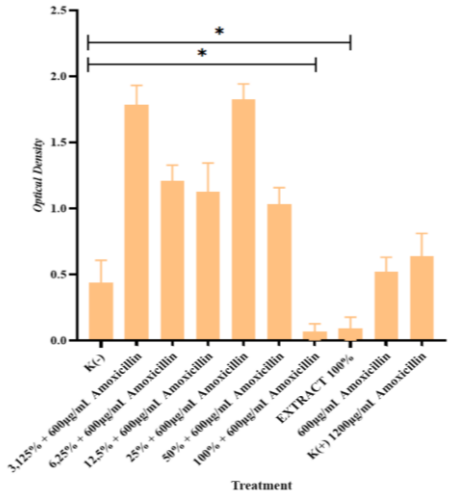
Figure 1. Antibacterial test results of *C. sinensis* peel ethanol extract against *S. aureus* using the plate count method



(A)



(B)



(C)

Figure 2. Antibiofilm test results; (A) at 1 hour incubation period against negative control, (B) at 3 hour incubation period against negative control, (C) at 24 hour incubation period against negative control.
*= significantly different ($p<0.05$)

Tabel 1. Results of phytochemical testing of ethanol extracts from *C. sinensis* peel

Secondary Metabolites	Results
Flavonoid	+
Alkaloid	-
Tanin	-
Saponin	+
Quinon	-
Steroid	-
Triterpenoid	-

DISCUSSION

Qualitative phytochemical testing of ethanol extracts from C. sinensis peel showed the presence of several secondary metabolites, including flavonoids and saponins. Both of these compounds, found in C. sinensis peel, are known to be biologically active and can aid antibacterial activity through different mechanisms.[17] The mechanism of action of flavonoids is divided into three categories, namely inhibiting nucleic acid synthesis, inhibiting cell membrane function, and inhibiting energy metabolism. The interaction of flavonoids with bacterial DNA can also cause damage to the permeability of bacterial cell walls, microsomes, and lysosomes.[18] The antibiofilm activity of flavonoids is also associated with their ability to penetrate the biofilm layer and disrupt the structural integrity of the extracellular matrix.[3] Saponins are known for their ability to inhibit bacterial DNA formation and increase lipid membrane permeability.[19] By binding to the lipid membrane, saponins can disrupt the integrity of the bacterial cell wall and membrane, causing leakage and cell death.[20]

The results of phytochemical testing may differ from previous studies due to several factors. Significant variations in climate, as well as the geographical location and altitude of areas where C. sinensis grows in various regions, also affect the genetic makeup and phytochemical

composition contained.[21] In addition, the choice of extraction solvent can also affect the results of phytochemical tests. Different solvents can produce and extract different secondary metabolites.[22] Methanol solvent was often used in previous studies because of its polar nature. However, this study used ethanol as a solvent because of its non-toxic nature, making it safe to use.

In the antibacterial test, the bar chart shows that bacterial colony growth increases with increasing extract concentration. This is likely because the extract alone does not work as well as amoxicillin in inhibiting the growth of *S. aureus* colonies. In previous studies using mature and immature ethanol extracts of *C. sinensis* peel with the diffusion method, no inhibition zones were formed at all concentrations observed. There are several factors that cause the lack of antibacterial effectiveness in this study, such as the content of aliphatic aldehydes, oxygen-containing monoterpenes and sesquiterpenes, and a lower pH compared to unripe orange peel, which is responsible for the antibacterial activity of *C. sinensis* peel.[23]

The best research results on the antibiofilm effect of *C. sinensis* peel ethanol extract combined with amoxicillin were seen during the 1-hour incubation period or in the early stages of pellicle formation, at which point *S. aureus* had already undergone reversible attachment. During the 24-hour biofilm incubation period or the biofilm maturation phase, a high concentration of extract is required, namely 100%, to reduce the OD result. This is because at this stage, the biofilm has formed completely and is 1,000-1,500 times more resistant than planktonic bacteria.[24] This indicates that the combination of extract and amoxicillin works well as an antibiofilm agent.

Throughout the incubation period in the antibiofilm test, it can be seen that the ethanol extract of *C. sinensis* peel alone has a significant difference from both the negative and positive controls and can effectively inhibit the formation of optical density produced by *S. aureus*. However, throughout the incubation period, it can be seen that amoxicillin alone as a positive control did not differ significantly from the negative control, so it can be said that amoxicillin has no antibiofilm effect. This may occur because of amoxicillin resistance to *S. aureus* biofilm.[12,25] There have been no previous studies supporting this, so testing the antibiofilm effect of a combination of C. sinensis skin ethanol extract and amoxicillin is expected to provide reference data for future research.

In antibacterial and antibiofilm testing, irregular increases were observed across all concentrations. These results were likely caused by inconsistencies in pipetting, resulting in non-homogeneous results that were difficult to interpret. This study had limitations in terms of time and cost, so further research is needed.

CONCLUSION

There is a combined antibacterial effect of 600 µg/mL amoxicillin with ethanol extract of *C. sinensis* peel against *S. aureus*, which works at concentrations ranging from 3.125% to 100%. The antibiofilm effect of a combination of 600 µg/mL amoxicillin and ethanol extract of *C.*

sinensis peel against *S. aureus* is most effective during the initial 1-hour incubation period of pellicle formation. Ethanol extract of *C. sinensis* peel at 100% concentration alone can inhibit the growth and formation of *S. aureus* biofilm better than when combined with amoxicillin.

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